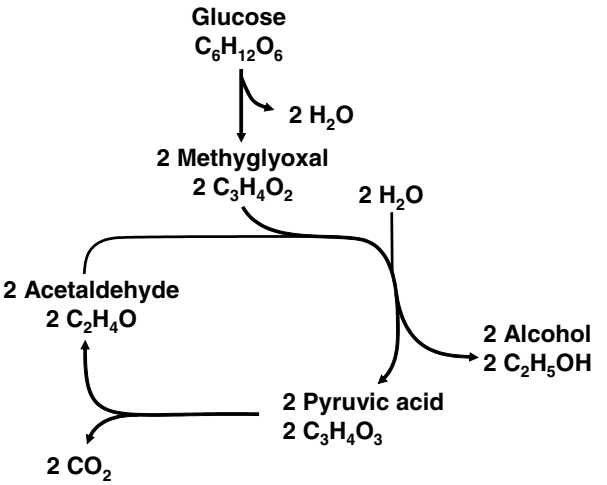

Figure 3.6. A representation of Neuberg and Kerb's proposed pathway of fermentation that brings out how it constituted a cycle.

was the focus of extensive research during the next fifteen years, much of it directed to showing that the proposed intermediates, especially methylglyoxal, really figured in the pathway. Because intermediates typically would not accumulate, indirect evidence was required. One critical issue was whether the intermediate would react to form alcohol at least as rapidly as glucose. Methylglyoxal failed this test, leading Neuberg to propose that it was an isomer of methylglyoxal that was the true intermediate.

Neuberg's proposal also failed to explain an additional finding concerning fermentation in cell-free extracts. Fermentation in such extracts typically slowed dramatically in a short time. Arthur Harden (1903) established that adding blood serum would produce an 80% increase in fermentation. Together with William Young, Harden further demonstrated that adding phosphate would also stimulate the reaction, which would then slow down again when the phosphate was exhausted (Harden & Young, 1908). They also established that the phosphate appeared to be taken up into a hexosediphosphate ester that itself could not be further metabolized but, as illustrated in Figure 3.7, would slowly decompose through hydrolysis. Neuberg dismissed this evidence, though, on the grounds that hexosediphoshate would not ferment in living cells (Neuberg & Kobel, 1925), thereby happily invoking the same argument strategy whose conclusion he resisted in the case of methylglyoxal. Harden and Young also demonstrated the need for addition of a "dialyzable substance which is not destroyed by heat" to maintain cell-free fermentation (1906, p. 410). Because heat destroyed the enzyme itself, this was obviously an additional substance;

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